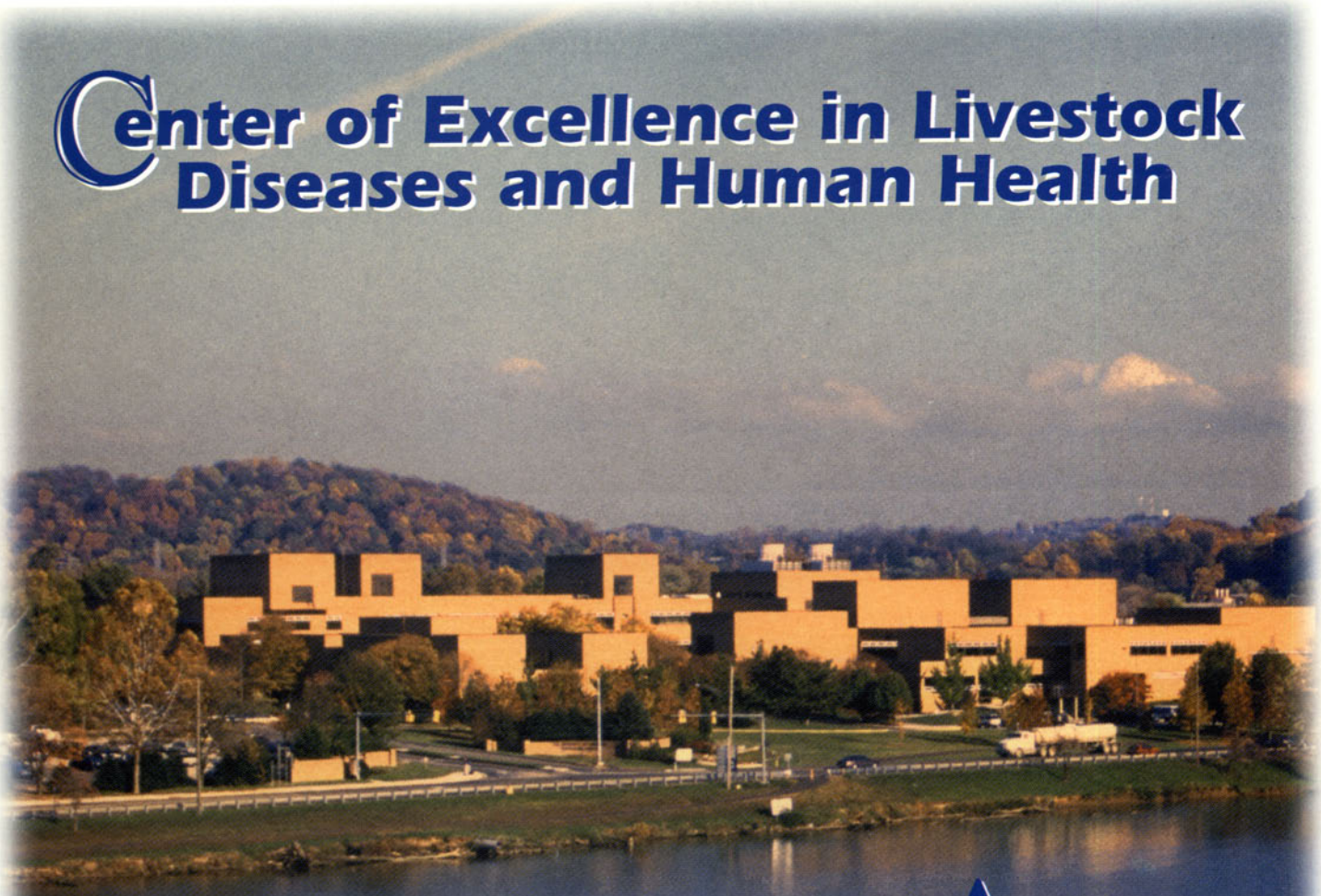
1999

Center for Excellence Annual Report, 1998-1999

College of Veterinary Medicine

Center of Excellence in Livestock Diseases and Human Health



Annual Report 1998 – 99

The University of Tennessee College of Veterinary Medicine, Knoxville

Table of Contents

DEAN'S MESSAGE

Dr. G.M.H. Shires, *Dean, College of Veterinary Medicine*

August 1999

The new format was so successful last year that Dr. Potgieter and his staff have worked hard to produce another attractive and informative report this year.

As you will note from the tables inside, our researchers once again produced a very impressive number of scientific publications–well over any benchmarks–and many researchers were invited speakers at important meetings of their peers nationally and internationally. Although funding has been very flat, the committee charged with review of proposals for funding has done a very thorough and fair job of selecting projects to be funded and equipment to be purchased out of the COE budget.

We have very recently added two primary researchers to our Center. These scientists both come with excellent records and a history of respectable funding.

We are indebted to all the scientists who contribute to the success of this COE as well as their supporting scientists and staff. Their efforts have made and continue to make the Center of Excellence for Livestock Diseases and Human Health a success story and a good investment for the Tennessee taxpayers. The COE provides a resource for the entire College and engages many other clinical and basic scientists in collaborative projects. This COE, therefore, plays a pivotal role in setting the pace for research in our College of Veterinary Medicine.

I appreciate the continuing support from the state of Tennessee as well as all those who work so hard to maintain the Center as an example to those who seek answers to some difficult problems in both animals and humans.

I hope that this report will be of interest to you and will inform you of continuing success of The University of Tennessee College of Veterinary Medicine Center of Excellence in Livestock Diseases and Human Health.

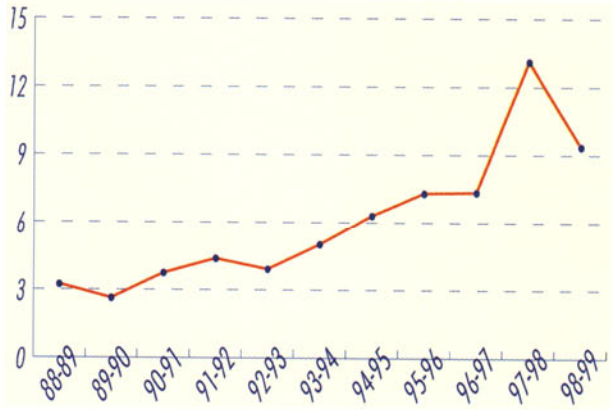
Sincerely,

G.M.H. Shires
Dean

PROGRAM REPORT

Dr. Leon N.D. Potgieter, Director of Research and Graduate Programs

It is my privilege to report on yet another productive year by the Center of Excellence in Livestock Diseases and Human Health for 1998. Once again the Center has met most of its objectives admirably. **The number of scientific communications in the form of refereed publications by Center-based investigators continues to be truly astounding (this year an average of 9.35 per participant** – see figure). Research results are disseminated to fellow scientists in prestigious, refereed international journals and to stakeholders in popular journals and magazines distributed regionally and nationally. **I am particularly impressed by the numerous invitations extended to several faculty in the Center to make keynote/plenary presentations at national/international scientific meetings.** They include Drs. S.P. Oliver, B.T. Rouse and T.W. Schultz.



Average Number of Refereed Scientific Publications by COE-Sponsored Investigators

A new format was used for annual report last year and was well received. This year I used the same format and have attempted to make some improvements. The report features the accomplishments and activities of investigators and research teams that constitute the core of the Center. Their achievements serve a crucial function in promoting the College of Veterinary Medicine, the Institute for Agriculture and the University of Tennessee. Furthermore, they continue to ensure that the Center maintains its strong competitive position and contribute to the fiscal health of our research environment. The report endeavors to emphasize the strength of the Center and give a clear indication of how it meets its objectives.

Accomplishments

The accomplishments and activities of most core laboratories in the Center are summarized in this report in a manner that can be comprehended by a wide readership. It should be evident from reading these synopses that the Center:

1. Improves the quality of human life by improving animal health.

2. Augments livestock disease research capabilities in the Institute of Agriculture.
3. Identifies and characterizes laboratory and animal models of important human diseases.
4. Studies animal/laboratory models for better understanding of human health.
5. Studies the mechanisms of disease development and characterizes causative agents of common diseases important to the State of Tennessee.
6. Improves the capabilities of the College of Veterinary Medicine, the College of Agricultural Sciences and Natural Resources and the Agricultural Experiment Station to manage these diseases.
7. Improves the facilities to enable the College of Veterinary Medicine to study more effectively infectious and toxic diseases of animals.
8. Disseminates through the Extension Service practical information required to reduce the incidence of livestock diseases.
9. Develops new strategies for the prevention of disease.
10. Improves facilities and expertise to enhance research training.
11. Develops innovative approaches to the treatment of human diseases.

Research Funding

An important goal of the Center of Excellence in Livestock Diseases and Human Health is to support researchers and to promote research by a variety of mechanisms. The Center of Excellence emphasizes the following six specific areas: **Infectious Diseases/Population Medicine, Toxicology, Reproduction, Host Defense, Molecular Genetics and Carcinogenesis.** The Center's underlying philosophy is to enhance the capacity of young or new investigators to compete for extramural funding and to assist established researchers in maintaining extramural support. The Center does not serve as a primary source of research funding for faculty. The main criteria used for funding proposals include scientific merit, likelihood of leading to extramural funding and relevance to the Center's objectives. Proposals submitted to the Center for funding are reviewed by the Research and Graduate Programs Advisory Committee. The latter has one representative from every department of the College of Veterinary Medicine and is chaired by Dr. Hildegard Schuller.

The Center supported the following projects over the past year:

1. **Drs. David Bemis and Stephen Kania:** Recombinant *Bordetella bronchiseptica* fimbrae as immunogens and carriers of unrelated antigens.
2. **Dr. David Brian:** Regulation of the coronavirus genome replication by two terminal genetic structural elements.
3. **Dr. James Godkin:** Retinoids in oocyte maturation and embryonic development.
4. **Dr. Kevin Hahn:** Inhibition of tumor growth and angiogenesis: Preclinical evaluation of cisplatin and minocycline in an osteosarcoma animal model.
5. **Dr. Lilitha Mendis-Handagama:** Thyroid regulation of precursor cell differentiation into Leydig cells in the rat testis.
6. **Dr. Jack Oliver:** Assessment of inflammatory and immunologic response of cattle to tall fescue toxins.
7. **Dr. Steve Oliver:** Characterization of the anti-phagocytic role of *Streptococcus uberis* M-like protein.
8. **Dr. Barry Rouse:** Immunopathology of herpetic stromal keratitis.
9. **Dr. Hildegard Schuller:** The MAP kinase cascade as a target for cancer intervention strategies with selectivity for small cell lung cancer.
10. **Dr. Terry Schultz:** Structure-activity relationships for environmental chemicals.
11. **Dr. Carla Sommardahl:** Chromosomal localization of modifier genes that vary the phenotypic expression of the *orpk* gene between the FVB/N and C3H mouse inbred genetic backgrounds; a mouse model for polycystic kidney disease.
12. **Dr. Hwa-Chain Wang:** Construction of malignancy-related molecular and cellular system for human breast cancer therapeutics.
13. **Dr. Erby Wilkinson:** Pancreatic stem cells.

Equipment and Facilities

Requests from 13 investigators for 23 pieces of equipment were funded by the Center of Excellence this past year. Researchers benefiting from the Center grants were Drs. Frank Andrews, Joseph Bartges, David Brian, Donita Frazier, Kevin Hahn, Alan Mathew, Lilitha Mendis-Handagama, Jack Oliver, Stephen Oliver, Barry Rouse, Hildegard Schuller, Terry Schultz and Hwa-Chain Wang.

Criteria considered in the allocation of these funds included justification of need, equipment availability in adjacent laborato-

ries, and the number of investigators who may benefit.

Renovations funded by the Center of Excellence include extensive repair and renovation of a walk-in cooler in A329A laboratory in the Veterinary Teaching Hospital. This cooler is used by numerous investigators supported by COE. Similarly, a venting problem identified with class II type B2 and class II type A hoods in A307A laboratory and in the P3 facility required extensive remodeling. This, and subsequent certification of these hoods, was funded by the Center of Excellence.

Student Awards

Becky Penrose, veterinary student

An important mechanism by which the Center of Excellence promotes biomedical research is to provide summer opportunities for veterinary students to do investigational work in research laboratories in the College of Veterinary Medicine. This past year the Center funded 9 requests from first- and second-year students. The students are required to provide a summary of their work which then is entered into a competition judged by Phi Zeta, the veterinary honorary society. This program is very successful. Several students presented their work to faculty and staff of the Institute of Agriculture (see Culture for Discovery) and at national scientific meetings. Numerous manuscripts detailing results from work done by these students have been submitted for publication to refereed journals. In fact, over the past four years, this program has resulted in 27 publications in refereed journals, several with the students as senior authors.

Personnel Changes

Recent recruitments of faculty with a significant research focus will benefit the Center of Excellence in the near future (see discussion on "Funding Levels"). Dr. Patricia Tithof was recruited by the Department of Animal Science. Her interest in vascular cell function and basic signal transduction pathways is in line with the Center's focus and appears to be an area that Dr. Tithof can exploit as a research niche for extramural funding.

Dr. David Slauson, head of the Department of Pathology, announced recently the successful recruitment of Drs Xuemin Xu and Mei-Zhen Cui. They bring with them significant research funding from NIH (R01 grants), American Heart Association and foundations. Their research interests also fall within the Center's focus.

Dr. Babette Fontenot was recruited to fill the position of Associate Director of the Office of Laboratory Animal Care. This

step should have a significant impact in facilitating research at the College of Veterinary Medicine.

Funding Levels

The total funding for the Center of Excellence has not changed significantly. Retirements and resignations have affected its growth for a few years now and therefore both extramural and state funds have remained steady. As can be seen from the "Research Funding" Section, 14 investigators participated in the Center this past year, compared to some previous years when more than 20 researchers were included in the Center. This has an impact on all Center of Excellence benchmarks. However, the state's investment in the Center of Excellence in Livestock Diseases and Human Health remains a healthy one. Extramural funding expenditures this year totaled $1,464,594; whereas the total funding level of all active grants and contracts supporting the Center amount to $7,612,922.

I am very encouraged that several faculty recently have secured new multi-year funding for COE-related research. They include:

Dr. Stephen Oliver: Dr. Oliver and his co-investigators have secured new funding on 10 grants totaling $1,058,992 from industry, foundations, producer groups and FDA. This includes a major grant ($475,610) from FDA for which Dr. Oliver serves as co-principal investigator on "Evaluation and use of BAM/FDA and rapid microbiological methods for on-farm surveys". Dr. Oliver is the principal investigator on eight of these grants and co-principal investigator on two.

Dr. Hwa-Chain Wang: Dr. Wang is a co-principal investigator in a National Institute for Dental Research Program Project Dr. Wang's contribution will be "Inactivation of the TGF-b receptor complex in oral cancer development". Total funding is $717,505.

Drs. Xuemin Xu and Mei-Zhen Cui: These investigators bring with them several extramural grants. Their total support from NIH, American Heart Association and foundations is $1,027,000. The primary R01 NIH grant is entitled "Role of apoE in Alzheimer's disease amyloid formation".

Culture for Discovery

In the past, the Center promoted a "Research Day" to showcase the achievements of participating faculty and to promote research at the College of Veterinary Medicine. Attendance

at this event has declined significantly in recent years. It appears that the format of scheduling an entire day or two for this event was not appropriate for local participation. This year the Center has sponsored regular seminars, posters and presentations by participating investigators and students. The program was advertised University-wide and has been very well attended and received. It seeks to foster interest in research and to display the Center's role in promoting research at the Institute of Agriculture. The following seminars were given:

Dr. Barry T. Rouse: Use of plasmid DNA for immunity and immunomodulation.
Dr. Hwa-Chain Wang: Intracellular signaling pathways from cellular transformation to apoptosis.
Dr. Jack W. Oliver: Pathophysiology of tall fescue toxicosis in cattle.
Dr. Hildegard Schuller: Mechanisms of lung carcinogenesis.
Terri Dolorico (veterinary student intern): Genetic detection of coronaviruses from primate and felid biologic samples.
Rebecca Penrose (veterinary student intern): Detection of *Borrelia burgdorferi* in white-tailed deer in the Great Smoky Mountain National Park.
Daniel Grove (veterinary student intern): Sedative and physiological effects of orally-delivered alpha-2 agonists in cats.

External Review

I look forward to another good year for the Center of Excellence in Livestock Diseases and Human Health. I am confident that the support provided by the Center for some of our promising investigators will constitute the embryogenesis of established research programs. I anticipate that the extramural funding and other benchmarks will make an incremental jump this year as a result of our strategic recruiting over the past two years (see funding levels). This should constitute an opportune time for reviewing our program. Therefore the periodic external review of the Center is planned for the coming year.

BORDETELLA LABORATORY

Drs. David A. Bemis and Stephen A. Kania
Fellow: Dr. S. Rajeev

Broncho-pneumonia and nasal deformity (atrophic rhinitis) are diseases of significant economic concern to hog farmers in Tennessee. Most of the tissue damage and clinical effects seen in atrophic rhinitis are due to a toxin produced by the bacterium *Pasteurella multocida* in nasal passages of swine. *Pasteurella multocida* can not easily colonize the respiratory tract, but *Bordetella bronchiseptica* does so readily and may also cause forms (usually milder) of disease. Of greater importance is the capacity of *Bordetella bronchiseptica* infection to pave the way for infection with other organisms, such as *Pasteurella multocida*. The introduction of *Pasteurella multocida* vaccines has greatly reduced the prevalence of severe atrophic rhinitis; however, in spite of the availability of commercial vaccines, *Bordetella bronchiseptica* infections remain widespread in pigs.

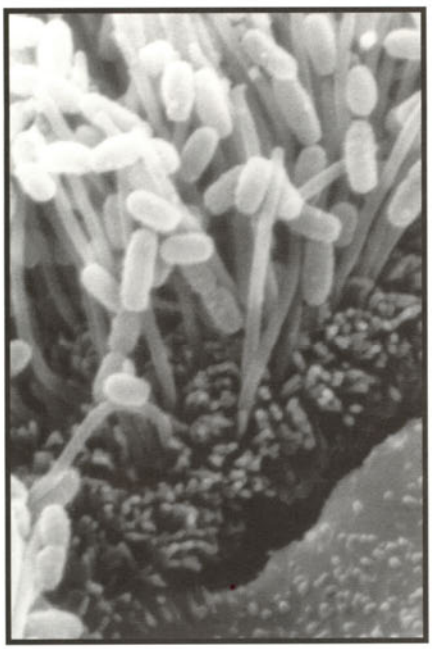
Dr. David A. Bemis and Staff

The main focus of the Bordetella Laboratory is the basic mechanisms by which *Bordetella bronchiseptica* colonizes the respiratory tract. The research concentrates on:

1. Identification of adhesins (bacterial structures responsible for attachment).
2. Examination of variations in bacterial strains and their effect on different hosts.
3. Production of protective immune responses against respiratory disease.

The impact of this research goes well beyond agricultural production enterprises because *Bordetella bronchiseptica* also infects dogs and cats, small laboratory mammals, horses, wild and exotic mammals and humans. It is closely related to *Bordetella pertussis*, the cause of whooping cough in humans. Better understanding of the mechanisms underlying *Bordetella bronchiseptica* colonization should identify improved strategies of prevention and therapy of bordetella infections and perhaps create novel methods for delivery of various vaccines and therapeutics to the respiratory tract.

Virulent *Bordetella bronchiseptica* organisms, when attached to ciliated epithelial cells, produce toxins that interfere with bacterial clearance from the respiratory tract. The Bordetella Laboratory has



Bordetella bacteria adherent to cilia of the epithelium lining of the trachea

developed laboratory organ and cell culture models to study the attachment process. The laboratory has determined that *Bordetella bronchiseptica* strains produce several distinct patterns of attachment and may have some specificity for particular animal hosts. This may explain the failure of specific vaccines to provide optimum protection against bordetella infections. Variations in attachment have been linked to variations in bacterial protein attachment structures. The Bordetella Laboratory identified an attachment-deficient *Bordetella bronchiseptica* strain that was also deficient in a protein present in certain surface structures called fimbrae. They reversed this deficiency by introducing the appropriate chromosomal DNA from an attachment-proficient strain. This research further supports a role of fimbriae in *Bordetella bronchiseptica* attachment. They subsequently identified, cloned and fingerprinted a new fimbrial gene (designated *fim*N). It appears to encode an important attachment protein of this bacterium and therefore constitutes a significant virulence factor and potential vaccine component.

The Bordetella Laboratory determined that these fimbrial genes also could serve as carriers of genetic material encoding substances capable of inducing immunity to other respiratory disease agents. They constructed genetic fusions between *fim*N and a portion of a protein from *Pasteurella (Mannheimia) hemolytica*. Such a chimeric protein was produced in a bacterial system that not only retained the immunity-inducing properties of their individual components, but also produced remarkably high yields of each component. The Pasteurella product produced by this means acquired a greater stability and elicited higher levels of antibodies in rabbits than was previously achievable with the individual predecessor. The capacity of this fimbrial protein to enhance the immune response and thereby to serve as an adjuvant has real applications to improve certain vaccines. The recombinant chimeric protein has immediate applications in the control of bovine pneumonia (shipping fever) caused by this organism. This research has resulted in a patent petition based on the capacity of this protein to serve as a vaccine to bordetella infections and as a fusion partner with other components to protect against a variety of pathogens.

In collaboration with investigators at Kansas State University and Drew University, the Bordetella laboratory has documented also the role of other surface bacterial structures (filamentous hemagglutinin and pertactin) in the attachment of Bordetella bronchiseptica to host cells. This work has advanced our knowledge of bordetella colonization mechanisms and offers promise that may provide new insights to the control of respiratory diseases.

VIRAL IMMUNOLOGY LABORATORY

Dr. Barry T. Rouse

Fellows: Staff and Graduate Students: Sangjun Chun, Shipa Deshpande, Seong Kug Eo, Uday Kumaraguru, Sujin Lee, Teresa Sobhani, Mei Zheng

Dr. Rouse's research deals with the recognition and interaction of the body with viral infections. This group has studied herpes simplex virus, an agent that affects over 80% of mankind, and persists indefinitely in infected individuals. Persistence occurs in the cells of the nervous system in the absence of detectable virus progeny or any other viral products. This type of persistence, known as "latency", is not permanent in all cells. Periodically some latently-infected nerve cells reverse their interaction, and new virus is produced. This may give rise to secondary lesions on the body surface at locations connected by nerve fibers to these nerve cells. Such recrudescent lesions occur frequently in some individuals and are the cause of considerable pain and distress. When occurring in the eye, they can cause a chronic inflammatory reaction (termed herpetic stromal keratitis), often resulting in blindness. Much remains unresolved regarding the nature of the interaction of herpes simplex virus with its host. One such enigma is that the reactivation episodes are clinically significant in some individuals, but unnoticed in others. A likely answer to this question lies in the effectiveness of one or more components of the immune defense system. However, it is a difficult phenomenon to study in the human host.

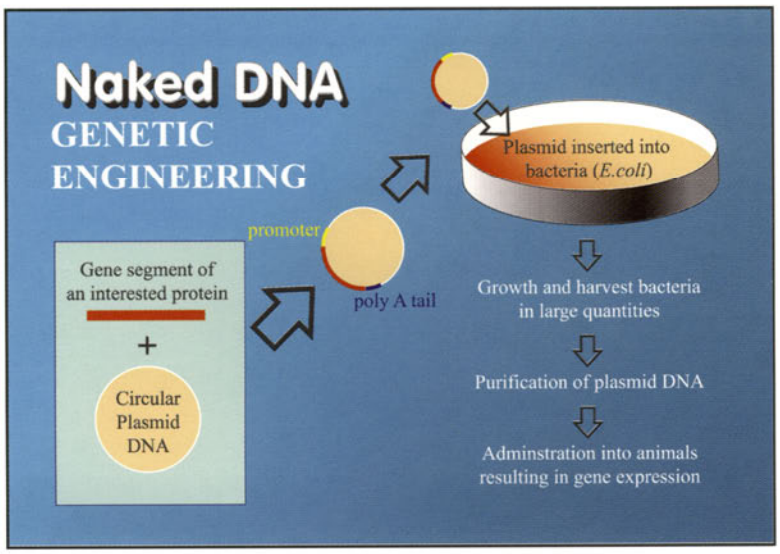
Dr. Barry T. Rouse

The Center of Excellence supports some aspects of this research which is funded primarily by substantial grants from the National Institutes of Health. This research has generated national and international interest, and the laboratory is recognized as one of the premier viral immunology programs in the country.

Value of Animal Models

Dr. Rouse's approach to understanding the interaction between HSV and the immune system has been to use model infec-

tions in experimental animals. The mouse, experimentally infected by this virus in a variety of routes, has proven to be an excellent animal model. Their aim is to understand how cells and molecular events set into play by herpes simplex virus lead to chronic inflammatory lesions or to resolution of disease. Ultimately, it may prove possible to manipulate the host defenses either to achieve protection by vaccines or resolution of injury by substances influencing the immune response introduced by gene transfer technology.



Currently, Dr. Rouse's major focus is to use novel vaccines composed of nucleic acids. These either encode genetic material of selected herpes simplex virus proteins or encode anti-inflammatory host response molecules to elicit protection or reduce severity of injury. In fact, they integrate the vaccine protection approach with the co-administration of molecules that can manipulate the quality of the immune responses induced.

Dr. Rouse has shown that certain molecules (cytokines) released from the body's own cells responsible for immunity (T lymphocytes), and other white blood cells, may profoundly influence crucial events during the induction of immune responses. Certain cytokines result in the prompt and effective immune resolution of virus injury, whereas other cytokines may lead to lesion exacerbation.

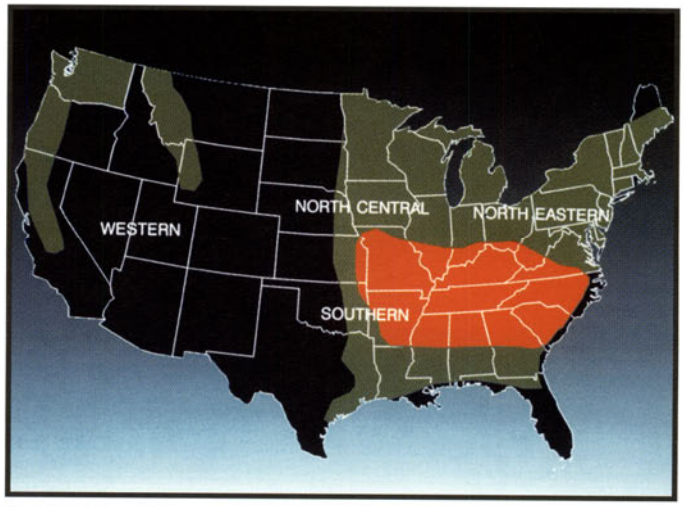
Dr. Rouse's group now is exploring the use of DNA (encoding various cytokines) given at different intervals in relation to either infection or immunization for their effect on the level of immune protection and disease expression. Their results are providing clues useful for the design of future herpesvirus vaccines and adjuncts for the therapeutic management of herpes lesions. They determined recently that one cytokine, IL-10, appears particularly useful for this purpose. Current research objectives are to compare a number of gene-transfer systems to produce IL-10 in animals for the purpose of understanding the mechanism by which this substance ameliorates virus injury.

It is hoped that the research will result in an understanding of the cellular and molecular steps that occur during ocular herpetic disease, and that clues will emerge that may improve the management of this common cause of blindness in mankind.

TALL FESCUE TOXICITY LABORATORY

Dr. Jack W. Oliver
Coinvestigators: Dr. Robert Linnabary, Dr. Eric Schultze, Dr. Bart Rohrbach.
Staff: Kim Abney, Elizabeth M. Bailey and Jane Czarra.

Tall fescue is the predominant cool-season grass grown in Tennessee and much of the Southeastern United States, and is a common forage for cattle and other grass-eating animals (herbivores). Most of the tall fescue grown in the U.S. is infected with a fungus (*Neotyphodium coenophialum*) that produces potent chemical agents known as ergot alkaloids. These alkaloids are harmful to livestock and result in serious economic losses to producers. The tall fescue toxicosis syndrome in herbivores is widely recognized as the primary grass-induced toxicity for animals in the U.S. There are more than 3.5 million acres of tall fescue in Tennessee representing approximately 10% of the total U.S. acreage. Annual animal production losses to the State due to consumption of the infected forage are estimated at 100 million dollars. Production losses in animals that consume contaminated tall fescue primarily occur due to severely impaired weight gain, milk production and reproduction.



Tall Fescue growth areas in the United States

A similar disease in humans has been known for hundreds of years and is associated with the eating of fungus-contaminated grains. This fungus (*Claviceps spp.*) produces ergot alkaloids similar to those present in infected tall fescue grass. It is common for tall fescue to be infested with both of these ergot alkaloid–producing fungi, increasing the toxicity level of the grass. Tissue injuries in people caused by ergotized grains were described in the 1930s, and outbreaks of a similar disease in cattle, associated with grazing on Kentucky 31 tall fescue, was identified in the 1950s. The incrimination of fungus contamination of tall fescue as the cause of toxicity in cattle was made by researchers at the University of Georgia in 1977. However, despite numerous studies at Southeastern Land Grant Colleges designed to understand and alleviate

the disease problem and intensive discourse among researchers worldwide, production losses continue in animals that graze fungus-infected tall fescue grass.

The long-term goal of Dr. Oliver's fescue research is to prevent the health problems in herbivores that consume the grass, while maintaining the drought and insect resistance imparted to the plant by the presence of the fungus (and ergot alkaloids). Development of an effective vaccine or chemical treatment is needed to counter the toxic effects in animals and thereby would allow full usage of this valuable forage. Alternatively, identifying the specific toxic alkaloids in tall fescue grass will allow plant scientists to genetically manipulate fescue grass to eliminate toxic alkaloid production.

Dr. Jack W. Oliver

Research on reducing severity of the disease by Dr. Oliver and co-workers has, among other advances, resulted in development of an effective anti-fescue toxicosis vaccine (U.S. patent awarded). The nutrient content of tall fescue is excellent, and this forage could be exploited even more widely if the associated health problems in herbivores could be prevented. The grass is a well-established, popular turfgrass and is valued for its vigor and root establishment, an important factor in preventing soil erosion.

The short-term goals of tall fescue toxicosis projects at the College have focused on injury to cardiovascular tissues of animals consuming fungal-infected tall fescue. Although much remains to be learned, excellent progress has been made. Dr. Oliver's work has established that vascular damage may be the central event induced by ergot alkaloids in animals. Their findings include:

1. The contractibility of blood vessels is increased by changes in blood vessel structure (alpha-adrenergic-2 receptors) that contributes to blood vessel narrowing.
2. Soluble chemical factors are consequently released by cells that line blood vessels and thus further stimulate vessel contraction and narrowing (thromboxane A_2, angiotensin II).
3. Circulating ergot alkaloids from fungal-infected tall fescue cause release of factors that promote blood clotting (Von Willebrand factor).

4. Damage to the lining cells of blood vessels and the associated attempt at repair (platelet aggregation and blood clotting), result in release of factors that cause vessel wall thickening (serotonin, thromboxaneA$_2$, angiotensin II).

As a consequence of injury to blood vessels, blood flow to tissues is impaired causing localized tissue damage and thereby affecting the function of body systems. Examples include:

1. Decreased blood flow to the skin affecting hair coat quality (unthrifty appearance) and contributing to heat stress in animals by interfering with heat loss from body surface.
2. Altered blood flow and blood clotting in the small vessels of lung tissues impairing oxygen distribution to tissues, and decreasing heat loss via the lungs.
3. Altered blood flow to mammary tissues contributing to decreased milk production.
4. Altered blood flow to reproductive structures affecting reproductive capacity.
5. Decreased blood flow to the intestines and the liver affecting nutrient intake, body metabolism and growth.

An important recent achievement by these researchers was the identification of definitive markers of fescue toxicity in cattle (after a three-year grazing study with twenty sampling times). This will be important to future studies in assessing treatment effectiveness (see below). These markers include:

1. Significant decrease of certain serum biochemical factors (cholesterol, total protein, globulin, fibrinogen and prolactin).
2. Significant increase of certain serum biochemical factors (creatinine, albumin and total bilirubin).
3. Significant decrease in certain serum enzyme values [alanine aminotransferase and alkaline phosphatase (from intestine and bone)].
4. Significant decrease in certain serum minerals (copper).
5. Significant alteration in red blood cell parameters (increased numbers, smaller size, decreased hemoglobin concentration).

USDA-supported studies by the group are continuing, and, in particular, are examining toxicity associated with purified alkaloids that are suspected of being the primary tall fescue toxins. To date, toxicity by individual alkaloids in isolated bovine blood vessel tissue systems in the laboratory (vascular endothelial and smooth muscle cells) has been marginal, indicating the probability that several alkaloids act in concert in animals (synergism). Similarly, prolonged treatment of cattle with ergovaline alone, an ergot alkaloid thought by many to be the primary tall fescue toxin, elicits only marginal toxicity. Thus, elimination of certain individual fescue toxins from grass may not totally eliminate the disease in animals, but can be expected to reduce toxicity by reducing the synergistic effect.

Current studies by Dr. Oliver and others are documenting that immune functions of affected cattle are suppressed. Antibody responses are reduced, phagocytosis (an important defense mechanism) is impaired and changes may occur in the character of cells that mediate immunity (lymphocytes). Thus, cattle that graze fungal-infected, tall fescue grass are at increased risk for development of infectious diseases.

A team of diverse scientists in Arkansas, Kentucky, Missouri and Dr. Oliver's group are preparing a proposal to be submitted to USDA for an interdisciplinary approach to study the pathobiology of tall fescue toxins, and to test treatments using a unique "Heat Stress Model". Although problems associated with fescue toxicosis have been known for decades, attempts at managing or treating the disease have been largely unsuccessful. This is due, in part, to the lack of a reliable animal model that allows for precise determination of the effect of tall fescue toxins on a variety of physiological/biochemical endpoints. The proposed research will develop this model in Angus cattle and exploit large animal heat chambers built at the University of Missouri and markers of fescue toxicity identified by Dr. Oliver's group to test effectiveness of anti-fescue toxicosis drugs and other treatments.

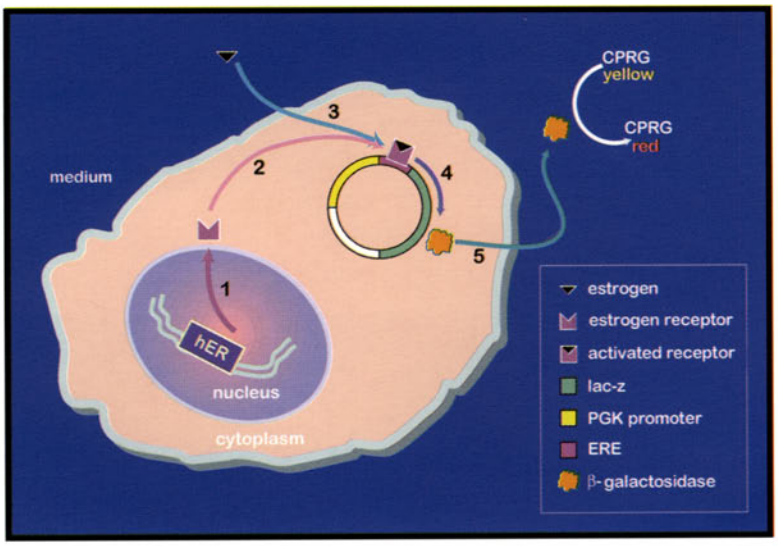
BIOLOGICAL ACTIVITY TESTING AND MODELING LABORATORY

Dr. Terry W. Schultz
Staff and Graduate Students: Glendon Sinks, Betsy Gregory, Julie Seward, and Elizabeth Hamblen

The Center of Excellence in Livestock Diseases and Human Health continues to support the Biological Activity Testing and Modeling Laboratory and the program of Dr. Terry W. Schultz. The long-term goal of Dr. Schultz's program is to develop structure-activity models and computer-aided, knowledge-based systems that will predict toxic/biological activity of chemical compounds from molecular structure. Structure-activity modeling is considered a reliable tool for hazard assessment. Dr. Schultz at the University of Tennessee's College of Veterinary Medicine is at the forefront of the development of this science. Structure-activity relationships correlate biological toxic/activity potency of chemicals to their chemical properties. Since properties of chemicals are related to their structure, structure-activity studies investigate the nature of chemical structure that will produce a well-defined biological response. During the past year the group has made significant improvements in the prediction of the toxic potential of certain chemicals (e.g. the successful modeling of the activity associated with electrophilic chemicals and skin-sensitizing agents). The current primary focus of this program is to develop a better understanding of chemicals that mimic certain hormones (e.g. estrogens). Many industrial, pharmaceutical, and natural products have the potential to mimic or interfere with hormone receptors on cells causing toxicities in people and animals. Numerous such toxicants elicit estrogenic or anti-estrogenic effects. Existing structure-activity testing for estrogenicity is based on the measurement of binding to estrogen receptors on cells. However, Dr. Schultz has shown that the mere binding to an estrogen receptor is not sufficient to determine if a compound is estrogenic, because of the inherent inability of such assays to distinguish between receptor agonists and antagonists.

Dr. Terry W. Schultz

Investigators in the Biological Activity Testing and Modeling Laboratory are attempting to standardize and validate an assay based on the metabolic activation of a yeast containing an estrogen receptor (the *Saccharomyces cerevisiae*-based lac-Z reporter assay as an *in vitro* assay allowing for the quantitative assessment of chemicals that alter estrogen receptor-mediated protein synthesis). The assay is very sensitive, rapid, and inexpensive. Work over the past year has focused on optimizing the sensitivity and accuracy of the test. Several parameters have now been established in the laboratory.



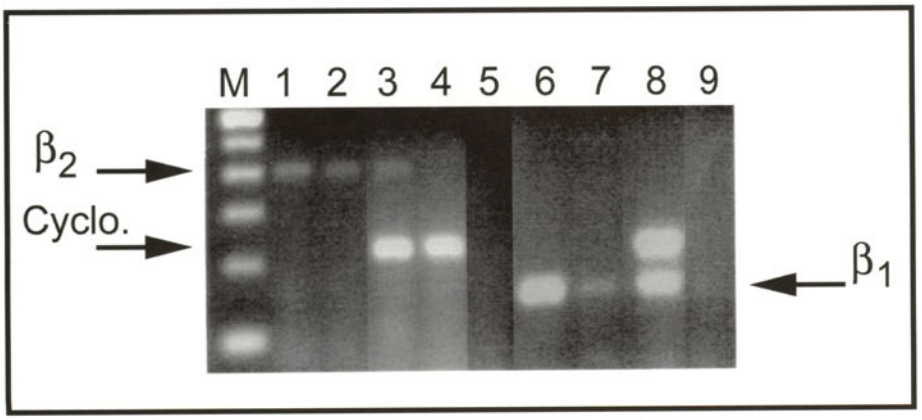
Lac-Z estrogen receptor activation assay.

Soybeans and their products contain estrogen-like polyphenolic compounds (phytoestrogens) such as isoflavones. In order to assure that food containing excessive quantities of phytoestrogens is not produced, careful screening of soybean varieties is merited. A novel analytical procedure has now been developed in Dr. Schultz's laboratory to evaluate estrogenic potency of soybean extracts. Using this technique, they were able to quantify the concentrations of certain estrogen-like compounds in the Bragg strain soybean. The procedure has been validated by comparison with standard (but laborious) chemical assays. A distinct advantage of this approach is the ability to estimate estrogenic activity from phytoestrogens in complex foods.

bronchiolitis, asthma, emphysema, and chronic obstructive pulmonary disease. This disease complex, which is often referred to as "allergies" has the same geographic distribution as lung cancer with which it shares some risk factors such as smoking and air pollution. Accordingly, East Tennessee, which has one of the highest lung cancer rates in the U.S., is also often referred to as "the land of allergies". For all lung cancer types, chronic lung disease has been identified as a risk factor even without a history of exposure to smoke.

Dr. Schuller's research has been dedicated to the study of lung cancer for over 20 years. It is her belief that effective strategies for the prevention and therapy of this disease complex can only be based on an in-depth understanding of the regulatory mechanisms which govern the growth of normal lung cells and the cancers arising from such cells. In contrast to other laboratories that are searching for the "magic molecular event" responsible for the genesis of all lung cancers, she hypothesized that different lung cell types and different types of lung cancer may be governed by different regulatory mechanisms, which in turn may be affected differently by known risk factors for the disease.

Dr. Schuller's achievements in lung cancer research have been recognized nationally and internationally. Her research has been supported by the Center of Excellence, but her primary support comes from substantial grants of the National Cancer Institute and the pharmaceutical industry.



Agarose gel demonstrating the expression of B1 and B2-adrenergic receptors in two cell lines derived from human lung adenocarcinomas. Our research has shown that these receptors regulate the growth of this particular lung cancer type.

Recent Achievements:

Dr. Schuller previously determined that high carbon dioxide levels found in individuals with chronic lung disease act as a potent activator of intracellular messengers (mitogen activated kinases) that stimulate cell growth in small-cell lung cancer. Her work also documented that these cells are regulated by a cell surface receptor (which is part of the autonomic nervous system) to which nicotine and cancer-causing nitrosamines (formed from nicotine) bind with high affinity. These tobacco-specific chemicals thus affect the cell's regulatory machinery to continuously stimulate cell growth. Together these findings explain why small-cell lung carcinoma is almost exclusively found in smokers with a

history of chronic lung disease.

Using a combination of molecular and pharmacological techniques, she recently determined that this cell surface receptor is a type of nicotinic acetylcholine receptor which polarizes the cell membrane. Dr. Schuller found also that 100,000 times lower concentrations of the tobacco-specific carcinogenic nitrosamine (NNK) than nicotine are required to activate this receptor. Her work further showed that this membrane depolarization caused the opening of multiple calcium-channels in the cell membrane leading to a massive influx of calcium from the extracellular environment. In turn, this massive increase in intracellular calcium resulted in the activation of multiple intracellular messengers of the kinase family, all of which stimulate cell growth. A comparison of the levels of expression of these calcium channels in small-cell lung cancer cells versus their normal cells of origin showed a massive over expression (stimulation or up-regulation) of these channels in the cancer cells. Collectively, these findings indicate that the chronic abuse of tobacco-products causes a massive increase of cellular calcium channels leading to the continuous overstimulation of multiple intracellular growth-stimulating pathways by the overabundance of intracellular calcium. Moreover, these findings suggest that calcium channel blockers which are widely used for the therapy of high blood pressure, may be promising drugs for the prevention and clinical management of small-cell lung cancer.

ANTICANCER MOLECULAR ONCOLOGY LABORATORY

Dr. Hwa-Chain R. Wang

Dr. Wang's long-term research goals concern the tumor-specific intracellular molecular signaling network and uncovering signaling pathways that can be induced by anticancer agents to lead cancer cells to programmed cell death (apoptosis).

His short-term goals are to identify intracellular signaling elements whose activation is involved in apoptosis induction of cancer cells. A corollary to this is to identify novel anticancer agents that may selectively induce apoptosis of cancer cells, while sparing normal cells. Ultimately he expects to apply the understanding of intracellular signaling control to anticancer therapeutics.

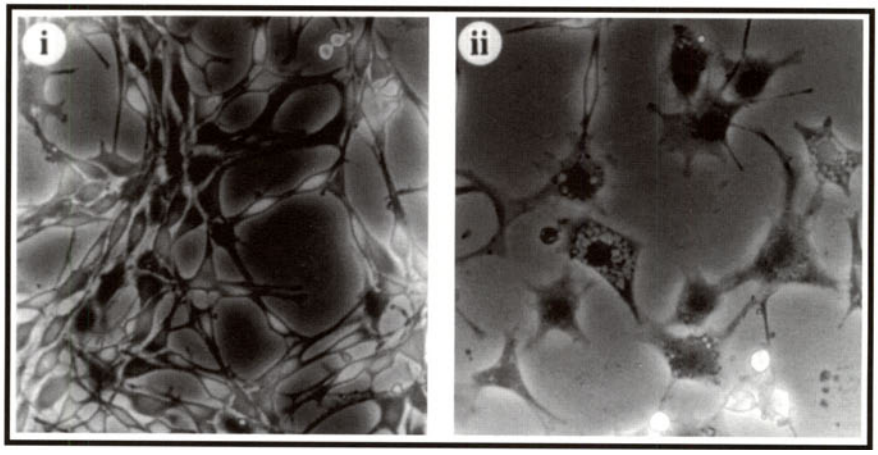
Dr. Hwa-Chain R. Wang and Staff.

Currently, Dr. Wang focuses on three approaches. The first is to understand the molecular and cellular function of a novel intracellular enzyme, which is activated in cells at the late stage of cellular malignancy (and in cells undergoing programmed cell death induced by forms of acute stress). The second is to study molecular and biological activities of a novel natural anticancer agent and how it selectively induces programmed cell death of cancer cells. The third is to develop a human breast cancer animal model involving inducible expression of various appropriate enzymes for study of anticancer agents on different stages of breast cancers.

Dr. Wang has identified a novel enzyme (kinase SAMK/Krs1) that is activated in cells at the late stages of transformation into cancer cells. The same enzyme is also induced in cells undergoing programmed cell death as a result of a variety of physiological, chemical or physical stresses. Dr. Wang determined that the gene encoding this enzyme might represent a member of a new kinase enzyme gene family. He is investigating the molecular and biological roles of this enzyme gene in cancer development and programmed cell death. Recently, he has detected also a related enzyme whose activation may be involved in arresting cell growth. Uncovering the apparent novel signaling

pathway that cross-links cancer development of cells to programmed cell death should be directly exploitable for development of anticancer therapeutics. This project is supported by a research grant awarded by the National Cancer Institute from 1998 to 2002.

Investigation into the molecular mechanisms of potential anticancer therapeutic agents on a variety of cancer cell types, particularly human breast cancer cells, is ongoing. Cancerous mouse embryo cells and various human tumor cells are used to screen anticancer agents. A novel natural substance isolated from bacterial cultures induces programmed cell death of these cells, but merely inhibits growth of normal cells. Studies on the molecular activities of this drug on different intracellular metabolic signaling pathways suggest it selectively induces programmed cell death of cancer cells. At least three important intracellular metabolic signaling pathways are affected. Dr. Wang has made progress in testing this phenomenon in cell cultures and is developing a unique model for testing in a mouse model. In the latter, he hopes to determine the efficacy of this anticancer agent at different stages of malignancy. His research is unique in that it links the molecular, cellular and animal system approaches in the development of anticancer agents. In collaboration with a clinical research group at The Ohio State University, he participates in a clinical phase I trial study of the anticancer agent.



Oncogene-transformed cells (left) are selectively induced by an anticancer agent to commit programmed cell death (right).

In collaboration with another research group at The Ohio State University, Dr. Wang also studies the molecular role of inactivation of a biologically-active cell surface molecule (the TGF-beta receptor complex) in oral cancer development. The collaboration has culminated into a program project grant funded in 1998 by the National Institute of Dental Research.

Dr. Wang's research is supported by the Center of Excellence, but his primary funding source is the National Cancer Institute.

TUMOR BIOLOGY LABORATORY

Dr. Kevin A. Hahn
Staff and Graduate Students: Dr. Yavuz Cakir, Valerie Brewer, Jason Yarbrough, Mary Ann Barnhill, Sharon West.

Many tumors and cancers can be treated effectively with certain drugs. Unfortunately resistance to several drugs is becoming a serious problem in cancer therapy. Dr. Hahn's hypothesis is that modification of the activity or function of certain enzyme systems (gluathione-S-transferases, matrix metalloproteinases) or cell membrane ion channels (sodium-bicarbonate-chloride channels) will result in the reversal of anticancer drug resistance and improve patients' response to therapy. Dr. Hahn's approach to confirming this hypothesis is to exploit a specific inhibitor of either of these systems and to determine whether drug resistance can be reversed.

Dr. Kevin A. Hahn

Work by Dr. Cakir (Ph.D. candidate in Dr. Hahn's laboratory) suggests that tetracycline antibiotics inhibit extracellular matrix metalloproteinases (MMPs). MMPs are enzymes which are located on the surface of cells. These enzymes digest the collagen fibers that hold cells together. Cancer cells and blood vessel forming cells produce increased amounts of these enzymes allowing them to migrate through tissues that results in cancer cell metastasis or new blood vessel formation.

Dr. Cakir's hypothesis is that tetracyclines will be useful in the treatment of cancer by either inhibiting tumor growth or tumor blood vessel formation, resulting in the palliation of clinical symptoms caused by the cancer. In another approach to achieve improved cancer therapy, Dr. Hahn with Jason Yarbrough (Master's Candidate) have shown that inhibiting the function of various membrane ion channels in cancer cells alters the cell's response to various anticancer drugs. In particular, blocking the cell's uptake of bicarbonate ion results in resistance to cisplatin chemotherapy.

Many cancer cells utilize energy inefficiently (anaerobic

glycolysis), resulting in the formation of excessive amounts of lactic acid. The body's response is to buffer this acid with a base (bicarbonate ions). The increase in bicarbonate ion concentration directly interferes with the uptake and intracellular activation of the anticancer drugs cisplatin, thus resulting in resistance to the therapeutic effects of cisplatin. Mr. Yarbrough is investigating the use of bicarbonate ion channel inhibitors as an approach to minimize cisplatin resistance in cancer cells located in an acidic microenvironment.

Finally, Dr. Hahn is collaborating with the University of Tennessee Medical Center Department of Surgical Sciences and the Department of Infectious Diseases in a project investigating the risk factors that may be associated with the onset of cellulitis (inflammation) of the breast following breast conservation surgical procedures for breast cancer. Rather than remove the entire breast in women with early stage breast cancer, only a limited portion is removed, followed by irradiation. This procedure is well-tolerated by most women but a small percentage develop complications several months later. Dr. Hahn and Valerie Brewer (Master's Candidate) have done a retrospective review of women with breast conservation therapy and comparing those women with cellulitis to time- and doctor-matched cohorts. It is anticipated that this epidemiological research project will identify pre-surgical or pre-irradiation risk factors associated with the onset of breast cellulitis. A prospective study will follow to confirm or deny the results of this retrospective study.

Dr. Hahn's research is funded, in part, by the Center of Excellence, the Morris Animal Foundation, the Companion Animal Fund, and the Bayer Corporation Animal Health Division.

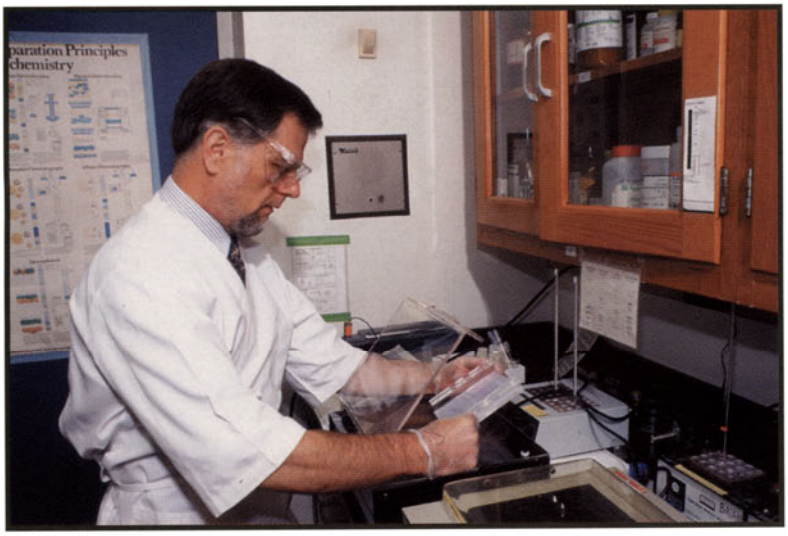
VIRUS MOLECULAR BIOLOGY LABORATORY

Dr. David A Brian

Fellows and Graduate Students: Dr. Savithra Senanayake, Dr. Jennifer Black, Dr. Aykut Ozdarendelli, Gwyn David Williams, Sharmila Raman

Dr. Brian's interest in basic molecular biology of viruses has resulted in discoveries of a fundamental nature for which his laboratory has received national and international recognition. His research focuses on coronaviruses which cause some of the most costly respiratory and gastroenteric diseases of livestock and fowl, and significant respiratory disease in people. Efforts to control coronavirus infections have been frustrated by three major obstacles:

1. An incomplete understanding of how coronaviruses replicate and persist in animals.
2. The ability of coronaviruses to rapidly mutate to new pathogenic variants.
3. The generally weak immune responses in animals to coronavirus vaccination and the logistical problem of inducing protective mucosal immunity in the vulnerable newborn.



Dr. David A. Brian

The primary research focus in Dr. Brian's laboratory is the molecular biology of coronavirus replication. With funding from the USDA and the NIH, and strategic support from the Center of Excellence, they are making an intense systematic effort to understand how five separate genetic structural elements of coronaviruses function to regulate production of viral proteins and progeny virus. This information should have significant impact in the design of new therapeutic strategies.

Of special interest is the mechanism by which a newly discovered element at one end (3′ end) of the virus genome (gene) regulates its replication. The element is a tRNA-like folded structure (a pseudoknot), that may regulate virus replication by binding to an important cellular protein that then becomes part of the virus replication machinery. Therapeutic interruption of such a virus-protein interaction would, in theory, lead to a cure of virus infection. Interestingly, the candidate protein in this interaction is histidyl tRNA synthetase, an autoantigen (normal tissue element causing an abnormal harmful immune response) in the human disease polymyositis.

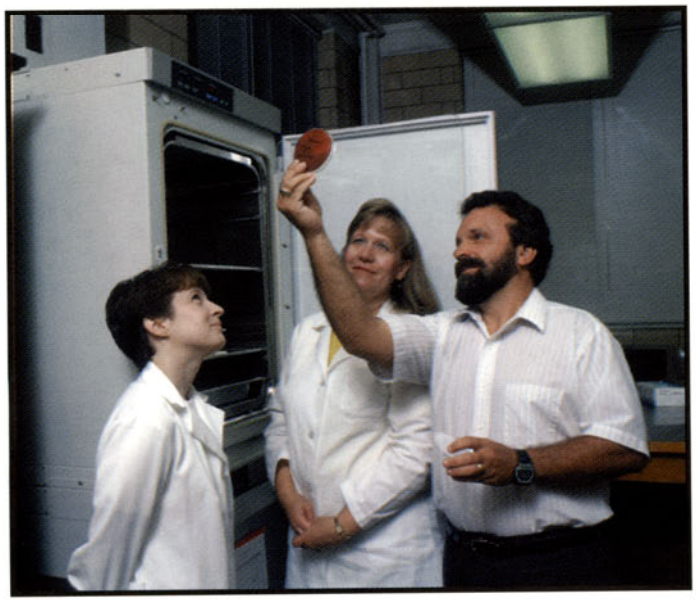
Dr. Brian and his group also have discovered a small variant of the bovine coronavirus genetic material (a viral minigenome) that replicates in the presence of wild-type virus. This minigenome is being experimentally engineered to carry many kinds of potential antiviral molecules into cells. One molecule is an enzyme (a ribozyme) designed to destroy the gene on which the virus depends for replication (the polymerase gene). This novel therapeutic approach may be able to cure a virus-infected cell without killing it.

MASTITIS RESEARCH LABORATORY

Dr. Stephen P. Oliver
Post-doctoral Research Associates and Staff: Raul Almeida, Weihuan Fang, Barbara Gillespie, Mark Lewis, Doug Luther, Susan Ivey, Lori Coleman.

Research conducted by Dr. Oliver focuses on mastitis in dairy cows caused by environmental organisms. Objectives are to:

1. Characterize factors which affect resistance of the udder to mastitis.
2. Characterize factors and mechanisms that permit mastitis pathogens to invade the udder and produce mastitis.
3. Develop and evaluate techniques for the prevention and control of mastitis in dairy cows.



Dr. Stephen Oliver and staff

He exploits an integrated approach to applied and basic research. Applied studies concentrate on issues of concern to the dairy industry that can have an immediate beneficial impact. This research includes strategies for controlling mastitis in heifers, and the influence of mastitis on reproduction of high-producing dairy cows. Basic research is aimed at discovering innovative methods of mastitis control exploiting biotechnological advances. This research includes development of nucleic acid probes for rapid and accurate detection of mastitis organisms and organisms responsible for food poisoning. Other studies being done concern virulence (severity) factors produced by and immunity to certain mastitis-producing organisms (*Streptococcus* species) in cows. They also are attempting to identify disease-resistant genes of dairy cattle.

Several kinds of bacteria are capable of infecting the udder causing mastitis. These pathogens invade the udder, mul-

tiply there and produce harmful substances that result in inflammation, reduced milk production and altered milk quality. Control of mastitis is extremely difficult because of the many types and sources of mastitis pathogens that can cause the disease. The National Mastitis Council estimates that mastitis costs U.S. dairy producers over two billion dollars annually. In Tennessee, losses due to mastitis may exceed $25 million annually. Thus, mastitis in dairy cows is likely the most costly disease affecting dairy producers in Tennessee, the U.S., and throughout the world.

Dr. Oliver was the first to show that mastitis in pregnant dairy heifers occurred frequently near calving and that many of these infections persisted into early lactation. His research has resulted in a simple, effective and inexpensive method for controlling mastitis in heifers. Intramammary antibiotic infusion before calving was shown to be an effective procedure for:

1. eliminating many infections in heifers during late gestation
2. reducing the prevalence of mastitis in heifers during early lactation
3. reducing the prevalence of mastitis in heifers throughout lactation.

He documented that a return of $12-$20 for each dollar spent was possible using this approach.

Several studies over the past 13 years at the UT Dairy Experiment Station involved collection of almost 200,000 milk samples for microbiological evaluation at intervals before calving, during lactation and during the dry period. Data from those studies have been computerized and this mastitis database may be the largest in the world. It now is being exploited for retrospective studies and will provide valuable information on the spread of mastitis pathogens, such as *Streptococcus uberis* and *Streptococcus dysgalactiae*, in high-producing dairy herds.

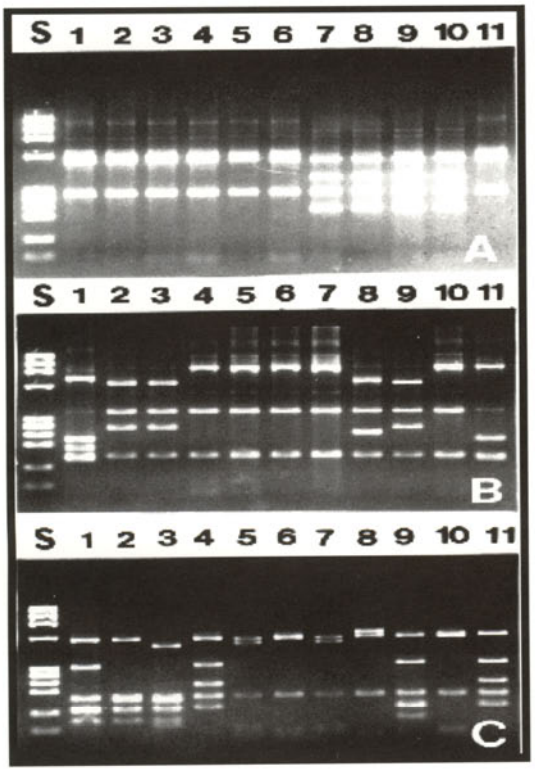
Recently, they evaluated the influence of mastitis on reproduction in Jersey cows and found it profoundly impairs reproduction during early lactation. Consequently, two proposals were funded recently by the American Jersey Cattle Association to delineate mechanisms by which mastitis can influence reproductive performance.

Dr. Oliver has been actively seeking the identification of virulence (severity) factors produced by certain mastitis organisms (*Streptococcus* species) and implications of immunity to them. In many dairy herds *Streptococcus uberis* and *Streptococcus dysgalactiae* are responsible for a high proportion of mastitis with

varying degrees of severity in lactating and non-lactating dairy cows. Strategies for controlling these mastitis pathogens are poorly defined and inadequate. This research focuses on:

1. genetic characterization of *Streptococcus uberis* and *Streptococcus dysgalactiae*
2. characterization of *Streptococcus uberis* and *Streptococcus dysgalactiae* with particular emphasis on factors involved in adherence and invasion into mammary epithelial cells
3. evaluation of immunity after immunization of dairy cows with components of *Streptococcus uberis* and *Streptococcus dysgalactiae*
4. effectiveness of experimental vaccines to *Streptococcus uberis* and *Streptococcus dysgalactiae* mastitis during the nonlactating period

Recently, Dr. Oliver's research group determined that *Streptococcus uberis* and *Streptococcus dysgalactiae* readily adhered to and invaded cells lining the bovine udder. Chronic infections then may develop, and their intracellular location may protect these bacteria from antimicrobial drugs and host defense mechanisms. Mastitis pathogens cultured in the presence of mammary epithelial (lining) cells in the laboratory synthesize proteins not detected when bacteria are cultured alone. These unique proteins likely are involved in virulence of bacteria, including their capacity to adhere and invade mammary epithelial cells. Thus, culture of mastitis pathogens in the laboratory in the presence of mammary epithelial cells may result in expression of bacterial virulence factors similar to that which occurs in the animal. This important discovery will be exploited for the development of vaccines and management of mastitis.



DNA Fingerprinting of Bacterial Pathogens

Dr. Oliver has communicated results of his research via scientific and popular press publications, and via presentations to several different target groups at state, regional, national and international meetings and conferences. In addition, Dr. Oliver has made several presentations to groups such as The University of Tennessee Agricultural Committee Board of Trustees, the Institute of Agriculture Development Board and the 21st Century Cam-

paign Steering Committee, Tennessee Agricultural Experiment Station Department Heads' Conference, and the Tennessee Higher Education Commission Center of Excellence Review team. This spring, Dr. Oliver has given presentations entitled "The University of Tennessee Mastitis Research Program: Making a Difference Through Research" to the Tennessee House of Representatives Agriculture Committee, to The University of Tennessee Institute of Agriculture Alumni Council, and to The University of Tennessee Institute of Agriculture Development Board and Agriculture Steering Committee for the 21st Century Campaign.

Dr. Oliver has increased the awareness of scientists, extension specialists, dairy producers, pharmaceutical companies and other members of the dairy community of the importance of environmental pathogens in bovine mastitis. Furthermore, he has discovered fundamentally-important information that is critical for controlling the heterogeneous organisms that cause mastitis Dr. Oliver's research philosophy is to design and conduct innovative and useful studies and to report to a wide variety of constituents. The ultimate goal of this research is to enable dairy producers in Tennessee, the U.S., and throughout the world to enhance the quantity and quality of milk produced and thus reduce the economic impact of mastitis.

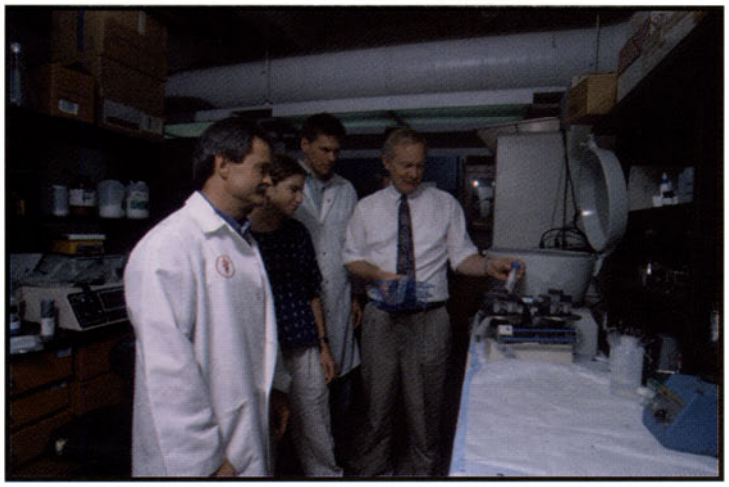
Dr. Oliver's research has been supported for several years by the Center of Excellence, but his primary funding has been derived from substantial grants from foundations and the pharmaceutical industry for several years. Recently, as co-principal investigator, he received substantial funding from the Food and Drug Administration.

RESEARCH TRAINING

Dr. David Slauson

The College of Veterinary Medicine funds at least ten positions for Ph.D.-level training of students with a professional medical degree. Some of these are based in the Department of Pathology (as part of their residency/Ph.D. program), and some are awarded without restriction. Most of these students become linked with investigators doing Center of Excellence-related research. The presence of this dynamic group of young investigators significantly bolsters the achievements of the Center. Faculty benefiting from these graduate students include Drs. Rouse, Schuller, Wilkinson and Potgieter.

In addition, the University of Tennessee College of Veterinary Medicine is one of few colleges of veterinary medicine to be chosen as a site for a National Institutes of Health (NIH) Institutional Training Grant. This 5-year training grant on the "Molecular and Cellular Pathobiology of Environmental Disease" is funded through the National Institutes of Environmental Health Sciences. The grant began in 1995 and is funded through 2000; current year funding is $145,270. This training grant is centered in the Department of Pathology, but also involves scientists from other departments as well as important collaborators in the Life Sciences Division at the Oak Ridge National Laboratory. These NIH funds provide stipend support for three years of advanced research training for DVM graduate students who already have at least two years of disease-oriented residency training. The research training sponsored by this new NIH grant emphasizes the basic molecular and cellular biology of disease, including environmental disease. The purpose is to produce well-trained individuals who understand disease at the tissue and whole animal level as well as at the most sophisticated edges of contemporary molecular and cellular pathogenesis. There are currently three DVM graduate students supported by these NIH funds and working in the laboratories of Center of Excellence-associated scientists.



Dr. David Slauson and graduate students

The summaries below illustrate the sort of quality individuals that we have been able to attract to the University of Tennessee with this NIH Training Grant:

Dr. Barbara Sheppard recently completed a Ph.D. degree in Dr. Hildegard Schuller's Experimental Oncology Laboratory on a project involving growth regulation of the cells of origin of small-cell lung cancer. Dr. Sheppard received her B.S. degree in biology from Virginia Polytechnic Institute in 1986 where she was on the Dean's List for her last 7 consecutive semesters. Dr. Sheppard then received a M.S. degree in physiology in 1989, also from VPI, and was awarded her D.V.M. degree from North Carolina State University in 1993. Dr. Sheppard was in private practice in Delaware for a year before entering the Pathology Residency Program at the University of Florida in 1994. Dr. Sheppard came to the University of Tennessee in 1996 to begin her graduate program. She now has joined the research team in the laboratory of Dr. David L. Rimm in the Department of Pathology at Yale University School of Medicine in New Haven, Connecticut. Dr. Rimm is an M.D., Ph.D. and is also Board-Certified in Anatomic Pathology and in Cytopathology. His successful and well-funded laboratory focuses on molecular and biochemical studies of the functions of cadherin-mediated adhesive interactions in metastasis, including genetic alterations in key regulatory proteins and receptors, and the molecular organization of the cell to cell interface.

Dr. Brian Jull is working on a Ph.D. degree in Dr. Schuller's laboratory, pursuing a difficult project that involves defining metabolic pathways involved in the regulation of growth of cells destined to develop into small cell lung cancer. Dr. Jull received his undergraduate degree in Animal Science cum laude from the University of Kentucky where he was a consistent member of the Dean's List. He received his D.V.M. degree summa cum laude, near the top in his class from the College of Veterinary Medicine at Auburn University in 1993. Dr. Jull was in a private practice in Kentucky before joining the pathology residency training program at the University of Tennessee in 1995. Dr. Jull was appointed as an NIH Postdoctoral Fellow at the University of Tennessee in 1997, and has approximately one more year to go to complete the Ph.D. degree.

Dr. Sharon Witonsky has been working in Dr. Erby Wilkinson's Cellular Pathobiology Laboratory on projects involving mouse models of genetic diseases. Dr. Witonsky was a Phi Beta Kappa undergraduate in biology and chemistry at Earlham College, and received her D.V.M. degree from the University of Minnesota in 1993 where she was an outstanding student. She came to the University of Tennessee College of Veterinary Medicine in 1993 as a graduate student, and has been engaged in research as well as clinical training in internal medicine here, aiming at specialty board certification and a Ph.D. degree in Comparative and Experimental Medicine. Dr. Witonsky was appointed as an NIH Postdoctoral Fellow in 1997. She finished her Ph.D. degree with Dr. Erby Wilkinson on a mouse model of Wiscott-Aldrich Syndrome last year and will be splitting her time between the University of Tennessee College of Veterinary Medicine and the world class immunology laboratory of Nobel Laureate Peter Doherty at St. Jude's Medical Center in Memphis. Dr. Doherty is an old friend of the college and has served on the Scientific Advisory Board for the college's Center of Excellence.

Beginning in July 1999, a new NIH Postdoctoral Fellow will be added for a one year appointment in order to complete his Ph.D. degree. **Dr. Steven Grubbs**, an American College of Internal Medicine Diplomate and graduate student in the Department of Comparative Medicine, will continue to work on a molecular epidemiology project in the laboratory of Dr. Leon Potgieter. This project involves the development of subgroup-specific and peptide-based ELISA's from the unique central hydrophobic region of ruminant respiratory syncytial virus G-glycoproteins. Dr. Grubbs will finish his Ph.D. degree within the next year.

It is hoped that the graduates of the NIH Training Program will be able to contribute to an enhanced understanding of the environmentally-caused disorders of man and animal both in terms of the morphologic expressions of disease and in terms of its molecular and cellular pathogenesis. We can all be proud of the trainees of this quality coming out of the University of Tennessee College of Veterinary Medicine.

DISSEMINATION OF RESEARCH TO THE GENERAL PUBLIC

Dr. Nancy Howell, Assistant Director, Communications

Although research findings from the Center of Excellence are distributed through peer-reviewed journals and professional meetings, an equally important goal is dissemination of these results to the general public. Distributing this information increases the public's awareness of the value of research and provides individuals with results that may improve their lives or their agribusiness.

The college exploits many resources to distribute information. It produces a general newsletter twice annually, distributed throughout Tennessee and beyond, which highlights research activities. Features on ongoing research, in addition to results from completed research, are included in the publication, Veterinary News, which is written for general audiences. Features appear in other University of Tennessee publications, including UT Agriculture, UT Alumnus and Tennessee AgriScience.

Television interviews with COE researchers, such as Dr. Steve Oliver, help to disseminate important research findings to the general public.

News releases are routinely distributed to state media, in addition to selected regional and national media. Television and print publications produce numerous features about the college each year, many related directly to research conducted through the Center of Excellence. Public displays about the college also frequently include highlights of COE research. In addition, Center of Excellence researchers are invited to share their research, not only professionally, but as speakers to commodity groups, civic groups and other interested individuals.

The World Wide Web offers another opportunity for information dissemination. Research news is a major component of the college's web site, and includes some COE projects, such as the status of tall fescue toxicity research at the University of Tennessee.

The distribution of research material in the general media not only helps inform the public, but allows the public to better understand the practical applications of science to their daily lives.

BENCHMARKS

Table 1
Center of Excellence in Livestock Diseases and Human Health
Benchmarks of Faculty Accomplishments
Faculty Members Associated with the Center of Excellence

	Year 5 (Final Year of Initial Commitment Center) 1988-1989			Year 6 (Year 01 as Accomplished Center) 1989-1990		Year 7 (Year 02 as (Accomplished Center) 1990-1991		Year 8 (Year 03 as (Accomplished Center) 1991-1992	
	Target	Actual	Avg	Actual	Avg	Actual	Avg	Actual	Avg
Number of:									
Articles		74	(3.22)	68	(2.62)	97	(3.73)	83	(4.37)
Books or Book Chapters		7	(0.30)	17	(0.65)	14	(0.54)	6	(0.32)
Published Proceedings		21	(0.91)	37	(1.42)	42	(1.62)	24	(1.26)
Total Publications	2.82	102	(4.43)	122	(4.69)	153	(5.89)	113	(5.95)
Abstracts	0.30	33	(1.43)	66	(2.54)	48	(1.85)	47	(2.47)
Invited Participation at:									
Regional Meetings	0.50	36	(1.56)	19	(0.73)	28	(1.08)	13	(0.68)
National Meetings	1.25	55	(2.39)	28	(1.08)	44	(1.69)	36	(1.89)
Faculty in Center		23		26		26		19	
Number of Visitors		10		17		17		12	

	Year 9 (Year 04 as Accomplished Center) 1992-1993		Year 10 (Year 05 as Accomplished Center) 1993-1994		Year 11 (Year 06 as (Accomplished Center) 1994-1995		Year 12 (Year 07 as (Accomplished Center) 1995-1996	
	Actual	Avg	Actual	Avg	Actual	Avg	Actual	Avg
Number of:								
Articles	78	(3.90)	95	(5.00)	132	(6.29)	153	(7.29)
Books or Book Chapters	7	(0.35)	9	(0.47)	5	(0.24)	5	(0.27)
Published Proceedings	17	(0.85)	11	(0.58)	37	(1.76)	65	(2.95)
Total Publications	102	(5.10)	104	(5.47)	174	(8.29)	223	(10.62)
Abstracts	53	(2.65)	55	(2.89)	42	(2.00)	64	(3.05)
Invited Participation at:								
Regional Meetings	15	(0.75)	18	(0.95)	41	(1.95)	55	(2.62)
National Meetings	47	(2.35)	47	(2.47)	65	(3.10)	70	(3.18)
Faculty in Center	20		19		21		22	
Number of Visitors	12		13		15		18	

	Year 13 (Year 08 as Accomplished Center) 1996-1997		Year 14 (Year 09 as Accomplished Center) 1997-1998		Year 15 (Year 10 as (Accomplished Center) 1998-1999	
	Actual	Avg	Actual	Avg	Actual	Avg
Number of:						
Articles	176	(7.33)	179	(11.2)	131	(9.40)
Books or Book Chapters	5	(0.21)	104	(6.50)	16	(1.10)
Published Proceedings	71	(2.96)	72	(4.50)	42	(4.50)
Total Publications	249	(10.38)	355	(22.2)	189	(22.2)
Abstracts	71	(3.01)	56	(3.50)	71	(3.50)
Invited Participation at:						
Regional Meetings	68	(2.83)	76	(4.80)	43	(4.80)
National Meetings	76	(2.92)	74	(4.60)	62	(4.60)
Faculty in Center	24		16		14	
Number of Visitors	18		19		11	

TABLE 2

RESEARCH PROJECTS FUNDED EXTERNALLY

REPORT PERIOD 1998-99

PROJECT DIRECTOR	TITLE OF GRANT	FUNDING AGENCY	TOTAL AWARDED	ESTIMATED EXPENDITURES
David Bemis	Antibody response to *Bordetella bronchiseptica* chimeric fimbrial protein antigen	USDA 1433 Funds	$12,000.00 10/01/98-9/30/99	$9,407.33
	Recombinant *Bordetella bronchiseptica* fimbriae as carriers of unrelated antigens	USDA 1433 Funds	$12,000.00 10/01/97-09/30/98	$5,802.60
David Brian	Bovine coronavirus vector for mucosal immunity to phaemolytica leukotoxin	USDA	$140,000.00 09/15/95-09/30/99	$1,388.34
	Mechanism(s) of coronavirus RNA replication and packaging	National Institute of Allergies and Infectious Diseases	$586,309.00 07/01/96-06/03/01	$130,402.93
James Godkin	Fetal maternal interaction	USDA	$189,970.00 09/93-08/98	$7,546.67
Thomas Doherty	Evaluation of splanchnic blood flow in normal and endotexemic horses	USDA 1443 Funds	$4,700.00 10/01/97-09/30/98	$3,214.14
Stephen Kania	Serum neutralization of bovine virus	Pfizer	$6,400.00	$2,671.20
	Development of control sera for canine serology	Pfizer	$5,120.00	0
Charmi Mendis-Handagama	Increasing the sperm counts in testes of bulls using the transient hypothyroid treatment	URCEO, France	$24,000.00 01/97-01-99	$1,567.86
Jack Oliver	Reactivity of bovine vasculature to Ergovaline and Ergine of toxic tall fescue	USDA	$188,000.00 10/01/97-09/30/00	$40,491.18
	Assessment of inflammatory and immunologic responses of cattle to tall fescue toxins	USDA 1433 Funds	$3,000.00 10/01/98-9/30/99	$3,000.00
	Vascular cell injury by toxicants of tall fescue grass	USDA 1433 Funds	$5,000.00 10/01/97-06/30/98	$141.00
Stephen Oliver	The prevention of mastitis in dairy cows by two novel postmilking teat disinfectants	Farnam Companies, Inc.	$24,828.00 2/96-3/98	$24,828.00
	Influence of prepartum intramammary infusion of pirsue or albacillin on mastitis and lactational performance of heifers during lactation	Pharmacia Upjohn	$50,000.00 .4/97-02/03	$17,865.76

PROJECT DIRECTOR	TITLE OF GRANT	FUNDING AGENCY	TOTAL AWARDED	ESTIMATED EXPENDITURES
Stephen Oliver	Evaluation of specific immune responses and protection by novel streptococcal antigens	Pfizer Company	$245,624.00 06/98-12/99	$46,683.34
	Lactation/mastitis research	General Mastitis Research Fund	$257,573.00 11/90-11/00	0
	Efficacy of extended pirlimcin therapy for treatment of chronic environmental streptococcus intramammary infections in lactating dairy cows	Pharmacia Upjohn	$38,000.00 6/98-12/98	$5,409.03
	Development of chronic *Streptococcus uberis* intramammary infections in lactating dairy cows using an experimental infection model	Pharmacia Upjohn	$38,000.00 01/99-12/00	0
	Lactation/mastitis research	Schattner Foundation, Inc.	$32,000.00 1999	0
	Evaluation of safety, specific immune responses, and protection against experimental infection in dairy cows following administration of *Streptococcus uberis* antigens in combination with rmLT	Pfizer, Inc.	$165,000.00 4/99-01/00	0
	A rapid specific test for Salmonella subtypes	National Pork Producers Council	$29,150.00 06/99-07/00	0
	Characterization of the antiphagocytic role of *Streptococcus uberis* M-like protein	USDA Formula Funds	$20,000.00 10/01/98-09/30/99	$20,000.00
	Evaluation of specific immune responses and protection	Pfizer, Inc.	$149,433.00 2/97-03/99	$48,069.33
Barry Rouse	Herpes zosterfilization	Smith-Kline Biological	$124,746.00 07/01/90-12/31/04	0
	Immunity mechanisms in herpesvirus infections	National Institute of Allergy and Infectious Diseases - NIH	$1,065,526.00 06/01/95-05/31/00	$265,791.33
	Mechanisms of herpetic stromal keratitis	National Eye Institute - NIH	$246,205.00 09/30/97-09/29/02	$215,557.59
	Biodelivery sciences	Biodelivery Sciences	$12,000.00 12/05/97-12/31/99	$1,206.30
	HSP peptide complexes as a putative vaccine against herpes simplex virus	Antigenics Agency	$16,620.00 04/15/99-04/14/00	0

PROJECT DIRECTOR	TITLE OF GRANT	FUNDING AGENCY	TOTAL AWARDED	ESTIMATED EXPENDITURES
Hildegard Schuller	Anticarcinogenic effects of Dexniguldipine-HcL in hamster	BYK Gulden	$401,300.82 02/01/92-12/31/99	$46,306.50
	NNK effects on receptor pathways	National Institute of Health	$663,700.00 01/01/94-09/30/98	0
	Regulation for the proliferative response of pulmonary neuroendocrine cells to nicotinic agonists	Verum Foundation for Behavior and Environment	$128,484.00 01/01/96-07/01/98	$7,385.22
	Transplacental pancreatic carcinogenesis by NNI	National Institute of Health	$1,001,479.00 09/01/96-07/31/00	$265,478.50
	Effects of the phosphodiesterase inhibitor B9302-107 on the nasal cavity in hamsters, mice and rats	BYK Gulden	$40,360.00 04/01/98-3/31/00	$520.00
	Mechanisms of action of the phosphodiesterase inhibitor Roflumiblast	BYK Gulden	$43,600.00 05/01/98-04/30/00	0
Terry Schultz	Development of a bioremediation risk assessment scheme	US Environmental Protection Agency	$59,199.00 09/94-09/98	$6,208.84
	Microbial transformation and molecular toxicology	Water Resources Research Institute	$59,000.00 10/97-09/00	$9,286.49
David Slauson	Cellular Pathobiology of Environmental Disease	NIH	$590,897.00 07/01/95-06/30/00	$111,622.22
Carla Sommardahl	Molecular analysis of PKD in the TGN737RPW mouse	NIH	$385,901.00 07/01/97-07/01/01	$64,420.84
Hwa-Chain Wang	Pathway leads to apoptosis in SCR-transformed cells	NIH	$517,520.00 01/01/98-12/31/02	$91,109.67

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